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Relationship between Clinicopathologic Features and Recurrence in Ovarian Germ Cell Tumor

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Abstract

Background: We conducted the present study to analyze the clinicopathologic features of patients with malignant ovarian germ cell tumor (MOGCT) with recurrence after 2 and 5 years.

Method: In this retrospective and analytical-descriptive study, the obtained data included: age, tumor size, histopathological type, tumor stage, lymph node involvement, laterality of tumor, tumor necrosis, and mitosis. We also evaluated the Cox Regression analysis between these variables with recurrence after 2 and 5 years.

Results: According to our exclusion criteria, we eliminated 81 cases. These cases consisted of the subjects with dysgerminoma (48.1%), immature teratoma (22.2%), yolk sac (16%), mix germ cell (11.1%), non-gestational choriocarcinoma (1.2%), and embryonal carcinoma (1.2%). We did not observe pure polyembryoma or polyembryoma in combination with mixed germ cell. All the patients received the treatment. The patients' mean age was 23.3±8.4 years. MOGCT reoccurred in 10 patients after 2 years and in 13 patients after 5 years (10 cases in the first 2 years, and 3 new cases in the next 3 years). Most of the cases (64.2%) were diagnosed to be at stage 1. The Cox regression analysis between positive lymph node and the recurrence of MOGCT after 2 years and between stage IV of disease and the recurrence after 2 years were significant. The Cox regression analysis between laterality, mitosis and necrosis in pathologic slides of the recurrence after 2 and 5 years was not significant.

Conclusion: Stages and involvement of lymph nodes are two major factors concerning the recurrence of MOGCT. Most recurrences occur in the first 2 years. Pathologic features (mitosis and necrosis) of MOGCt in the time of diagnosis not correlated with the recurrence of the disease.

Keywords: Clinicopathologic, Ovarian germ cell tumor, Recurrence, Prognosis

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Introduction

Ovarian cancer is one of the most prevalent types of cancer in women.[1] Malignant ovarian germ cell tumor (MOGCT) is a type of ovarian tumors accounting for 5% of all the ovarian tumors and about 25% of the malignant tumors of the ovary.[1, 2] This type of tumor has different subtypes and originates from primordial germ cells of the embryonic gonad.[3] Ovarian germ cell tumors (OGCTs) usually occur in young people under 30 years of age.[4, 5] Germ cell tumors are more common among Asian/Pacific Islander and Hispanic women than that in Caucasians.[6] These cancers are generally curable and have a good prognosis. However, without treatment, they are very aggressive. The important factors in an efficient prognosis of these patients are the time of diagnosis, surgery, and chemotherapy in the early stages of the disease.[7, 8] The study of the relationship between pathologic features, such as mitosis and cell necrosis with recurrence, has been carried out on certain cancers, and a relationship has been reported between these factors and recurrence in some of these cancers.[9, 10] However, the relationship between various pathologic features and recurrence in MOGCT remains unknown and there are no studies on this issue. Given that these tumors are low in prevalence and affect most young people, establishing a database regional for these tumors and identifying different determining prognostic factors for these tumors could be valuable. On the other hand, there are no studies on the association between the histological features and the recurrence of these tumors. Moreover, there are no studies on the prevalence and regional information of these tumors in southern Iran. Accordingly, the current study aimed to investigate the relationship between clinicopathologic features of patients with MOGCT with recurrence after 2 and 5 year.

Materials and Methods

This was a retrospective and analytical-descriptive research. We evaluated the patients with malignant ovarian germ cell tumors (MOGCT) referring to Shahid Motahari Tumor Clinic of Shiraz, Iran (southern Iran). The data were collected from our participants between 2002 and 2013 in the tumor clinic. All the patients had surgical treatment and some had received chemotherapy on top of the surgery.

Ethical approval

This study was approved by Shiraz University of Medical Sciences.

Inclusion/exclusion criteria

All the patients with any kind of malignant germ cell tumors included in the study.

Patients who showed no germ cell tumors in reviewing the pathology and died for other reasons (For example, myocardial infarction or accident) were excluded.

Gathered data

The collected data included: age, tumor size, histopathological type tumor stage, lymph node involvement, laterality of tumor, tumor necrosis, and mitosis.

The pathologic slides of all the 86 patients were obtained and re-examination was done by an expert pathologist. Subsequently, we reported the histopathological type, mitosis, necrosis, and lymph node involvement in the slides.

The information regarding laterality and size was gathered based on the operation notes, and the other data about mortality and morbidity. The data concerning the recurrence of MOGCT after 2 and 5 years of diagnosis were collected based on documentation of the clinic. The tumor stage was assigned using the International Federation of Gynecology and Obstetrics (FIGO) 2014. The staging system for ovarian cancer[11] was done based on operative reports. An expert pathologist performed the re-evaluation of the slides.

Data analysis

The statistical analysis was carried out utilizing SPSS software version 22 and the by Cox regression was performed (significance level: $P < 0.05$).

Results

Among 685 patients suffering from ovarian cancer, 86 patients were treated and followed up with the diagnosis of MOGCT. Following the

revision of pathologic slides by an expert pathologist, three of these cases were excluded due to the changes in diagnosis. We were compelled to eliminate two cases due to incomplete information and poor follow-up. In general, MOGCT accounted for 12.11% (83 patients) of all the ovarian cancers in our center. These 81 cases were as follows: 39 cases with dysgerminoma (48.1%), 18 patients with immature teratoma (22.2%), 13 patients (16%) with yolk sac tumor, 9 cases with mixed germ cell tumor (11.1%), 1 case with non-gestational choriocarcinoma (1.2%), and 1 case with embryonal carcinoma (1.2%). We have not seen pure polyembryoma or polyembryoma in combination with mixed germ cell. As mentioned earlier, we had 9 cases of mixed germ cell tumor, out of whom 7 had component of yolk sac tumor, while in 2 of them, immature teratoma was seen.

Most of the cases (64.2%) were diagnosed to be at stage 1. The recurrence of MOGCT after 2 years occurred in 10 patients, while it happened in 5 years in 13 cases, (10 of cases in the first 2 years, and 3 new cases had in the next 3 years). In these 5 cases, both ovaries were involved by the tumor. In 32 cases, we observed left ovary involvement, and in 40 cases, right ovary was involved by tumor. The laterality of ovarian involvement in four patients was unknown, because one case of dysgerminoma was seen in the retroperitoneal region without ovarian involvement, and in 3 cases, laterality of ovarian involvement was not reported. The patients' age at the time of diagnosis, ranged from 12-60 years; the mean of age was 23.3±8.4. 20 patients underwent the surgery alone and 61 received chemotherapy on top of the surgery (Table 1).

Table 1. Prevalence of variables

	Frequency	*Percent*
Age(year)		
10-20	29	35.8
20-30	36	44.4
30-40	13	16
>40	3	3.7
Subtype		
Dysgerminoma	39	48.1
Immature teratomas	18	22.2
Yolk sac tumor	13	16.0
Choriocarcinoma	1	1.2
Embryonal carcinoma	1	1.2
Mixed germ cell tumor	9	11.1
Stage		
I	52	64.2
II	7	8.6
III	17	21.0
IV	5	6.2
Lymph node involvement		
Negative	74	91.4
Positive	7	8.6
Laterality		
Right	40	49.4
Left	32	39.5
Bilateral	5	6.2
Unknown	4	4.9
Necrosis		
<10%	28	34.6
10%-50%	22	27.2
>50%	31	38.3
Mitosis		
<10%	28	34.6
10%-20%	15	18.5
>20%	38	46.9
Recurrence after 2 year		
Yes	10	12.3
No	71	87.7
Recurrence after 5 year		
Yes	13	16
No	41	50
Unknown	27	34

Grading was reported only in immature teratoma. Eight cases out of 18 patients with immature teratoma were diagnosed as high-grade in pathologic evaluations.

For the evaluation of the correlation of each variable with the 2 and 5-year survival, we employed Cox regression and hazard ratio (HR) report. Correlation of each variable was checked with recurrence after 2 and 5-year.

Due to the small number of patients, Cox regression was not used for evaluating the effect of grade on the survival of germ cell tumors.

The Cox regression analysis concerning the association between age (all groups) and 2 and 5-year recurrence risk was not statistically significant ($P > 0.05$).

Based on the Cox regression analysis regarding the relationship between any subtypes of germ cell tumors and 2 and 5-year recurrence risk, we observed no statistically significant differences

Table 2. The Cox regression analysis of age, tumor size, histopathological type, tumor stage, lymph node involvement, laterality of tumor, tumor necrosis, and mitosis effects on 2 and 5-years survival

	Survival after 2 years		Survival after 5 years	
Age(year)	HR	P-value	HR	P-value
10-20	11073.585	0.960	6549.815	0.969
20-30	7846.426	0.961	2900.632	0.972
30-40	5281.248	0.963	5269.000	0.968
>40	6028.451	0.971	4236.125	0.971
Tumor size				
	0.968	0.461	0.968	0.461
Subtype				
Dysgerminoma	0.462	0.528	0.23	0.3
Immature teratomas	1	1	0.000	0.98
Yolk sac tumor	2.77	0.362	0.692	0.79
Choriocarcinoma	9	0.12	0.000	0.99
Embryonal carcinoma	0.000	0.988	0.000	0.99
Mixed germ cell tumor	--	--	--	--
Stage				
I	1.094	0.567	0.000	0.981
II	0.000	0.99	0.000	0.992
III	2.294	0.277	0.000	0.987
*IV	*7.8	*0.007	5.2	0.178
Lymph node involvement				
Negative	--	--	--	--
*Positive	*4.53	*0.029	5.286	0.174
Laterality				
Right	0.375	0.396	30209.81	0.976
Left	0.781	0.822	18881.13	0.977
Bilateral	0.589	0.532	22698.22	0.976
Unknown				
Necrosis				
<10%	1.505	0.658	111741.126	0.955
10%-50%	1.273	0.809	99867.857	0.967
>50%	2.71	0.222	141747.926	0.966
Mitosis				
<10%	1.958	0.452	1.225	0.856
10%-20%	1.867	0.533	0.000	0.989
>20%	2.211	0.331	1.474	0.752

*P<0/05 was considered significant
HR: Hazard ratio

($P > 0.05$).

According to the Cox regression analysis, the relationship between tumor size and 2 and 5-year recurrence risk was not statistically significant ($P > 0.05$).

The Cox regression analysis concerning the association between IV stage of the disease and its recurrence after 2 years was statistically significant ($P < 0.05$); whereas, it was not statistically significant between other stages of the disease and 2 and 5-year recurrence ($P > 0.05$).

The Cox regression analysis indicated that the association between lymph node involvement and 2-year recurrence risk was statistically significant ($P < 0.05$), yet its association was not statistically significant with 5-year recurrence risk ($P > 0.05$).

The Cox regression analysis about the relationship between laterality and 2 and 5-year recurrence risk was not statistically significant ($P > 0.05$).

According to the Cox regression analysis, there were no statistically significant differences concerning the association between the rates of necrosis (all groups) and 2- and 5-year recurrence risk was ($P > 0.05$).

The Cox regression analysis regarding the correlation between the rates of mitosis (all groups) and 2- and 5-year recurrence risk illustrated no statistically significant differences ($P > 0.05$).

Table 2 presents the Cox regression analysis of age, tumor size, histopathological type, tumor stage, lymph node involvement, laterality of tumor, tumor necrosis, and mitosis effects on 2- and 5-year survival.

Discussion

In the present study, we brought all the cases of germ cell tumors who referred to Shiraz University tumor clinic from 2002 to 2013. There were 81 cases constituting a large group with a rare neoplasm.

In the study by Modarres Gillani, between 2001 and 2003, the authors reported that MOGCT was 17.1% of all the ovarian cancers in Tehran.[12] In another study, the prevalence of MOGCT in 2005-2006 in Iran was reported to be 13.8%.[13] The incidence of MOGCT ranged between 1 and 6% as reported in the West, and between 8 and 19% in Asia.[14] In the present study, which was conducted in southern Iran, MOGCT was 11.82% of all the ovarian cancers.

In an Arab study, 78% of germ cell tumors were found in patients below 30 years of age and the germ cell tumor incidence rate showed two peaks; in the age group of 20 - 29, and in the age group of 70 - 79.[13] According to Solheim study, between 1978 and 2010, 2541 women were diagnosed with MOGCT as their first-lifetime malignancy. The patients' median age at the time of diagnosis was 22 years, 91% of them being <40 years old. An important finding in this study was the adverse impact of the increase in age on the survival rate.[14] In a study by Sirvan in Thailand, who evaluated 130 patients diagnosed with MOGCT, the mean age was 21 years.[15] In our study, most of the participants aged between 20-30 years old. This suggests that these tumors mostly occur in young ages. Regarding the distribution of age, our results were in line with those of other studies; yet ageing was not a prognostic factor.

In the study by Smith, from the United States national cancer, from 1973-2002, 1262 cases of MOGCt were reported, which were histologically as follows: dysgerminomas (32.8%), immature teratomas (35.6%), mature teratomas with malignant degeneration (2.9%), endodermal sinus (14.5%), embryonal (4.1%), choriocarcinoma (2.1%), and mixed germ cell tumors (5.3%).[16] In another study, Hanan in 2015 reported 66 patients from 1994-2007, among whom dysgerminoma was the most common diagnosis (22 patients) before teratoma (16 patients), yolk sac tumor (15 patient), and mixed germ cell tumor (12 patient). Meanwhile, embryonal carcinoma was identified in only one patient.[17] The histological findings of Ghaemmaghami, in Vali-e-Asr Hospital of Tehran, Iran during 1997–2004, were immature teratoma (33.3%), mixed germ cell tumor (33.3%), yolk sac tumors (19%), and embryonal carcinoma (14.2%).[18] In accordance with Smith's study, in our study, 81 patients suffered from different subtypes of germ cell tumors, including dysgerminoma (48%), immature teratoma (22%), yolk sac tumor (13%), mixed germ cell tumor (11%), with embryonal carcinoma, and choriocarcinoma that was found only in one patient.[16] In this study, there were no correlations between the histological type and the recurrence of the disease.

Concerning stage, Haidari in a study in Washington University indicated that most OGCTs (67.3%) were in stage I.[19] Silva in 2015, at Brazilian national cancer institute with a ten-year experience, concluded that advanced stage and persistence of the disease were the important risk factors for survival.[20] In a study by Ertas, stage distributions at diagnosis for stages I, II, and III OGCT were 84.3, 5.4, and 9.3 %, respectively, and stage status was significantly associated with recurrence.[21] A study by Murugeasu showed for the first time that advanced stage and elevated HCG and AFP are independent

adverse prognostic factors in the patients with MOGCT. In addition, the elevation of both HCG and AFP were observed to substantially increase the risk of treatment failure. This is relevant to the management of MOGCT since it helps to identify which patients may require more intensive therapeutic strategies.[22] In our study, 64% of the subjectst were in stage I of the tdisease at the time of diagnosis, and only stage IV of this disease was associated with 2-year recurrence.

In this study, all the patients underwent the treatment and our survival rate was 100%, which was similar to the study of Weinberg in the USA reporting an overall survival rate of 100% among patients with both local and advanced MOGCT.[23] In Smith's study, the survival rates were lower for older women with no dysgerminoma subtypes.[16] In an Arab study, the 5-year survival rate of germ cell tumors was 85%.[24] In the SIRIVAN study, 5-year survival and overall survival were 82.4% and 92.4%, respectively.[15] In the follow-up of the patients in our study, 10 experienced the recurrence in 2 years from the start of the disease, and 13 subjects experienced the recurrences in 5 years, 3 of whom were added to the previous 10 patients. MOGCT had an excellent prognosis in all the stages.

Bilateral OGCT is normally associated with advanced-stage diseases, high-risk histology, and poor survival. Once other prognostic factors were considered, laterality was not the independent prognostic predictor of survival.[19] In our study, laterality was not related to recurrence.

Kumar, in a study in 2008, indicated that the 5-year survival rate with nodal involvement was significantly worse compared with the absence of lymph node metastasis; the involvement of lymph nodes was reported as an independent predictor of poor survival in these patients.[25] In our study, 91% of the patients had no lymph node involvement. The lymph node involvement and higher stage, separately, had an effect on 2-year survival in our study, but did not correlate with 5-year survival. This might be due to the sample size.

We could not find a study that evaluated the relationship between histological characteristics with the recurrence of this disease. Herein, the evaluation of the pathologic features (mitosis and necrosis) of tumor revealed no relationships with its recurrence. Furthermore, the tumor size was not found to be correlated with the recurrence. Therefore, it could be concluded that the increase in the tumor size could not increase the tumor recurrence after 2 and 5 years.

Conclusion

MOGCT survival rate is 100% with treatment. The stage of the disease and involvement of lymph nodes are two factors of great importance in the recurrence of MOSCT. Most recurrences occur in the initial 2 years of MOGCT diagnosis. The pathologic features (mitosis and necrosis) of MOGCT at the time of diagnosis are not correlated with the recurrence of disease.

Conflict of Interest

Nonce declared.

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